REMARKS

Pursuant to the Amendment filed on June 8, 2009, claims 1, 2, 4-8, 11-13 and 15 were amended, and claims 3 and 17-22 were cancelled.

Therefore, claims 1, 2 and 4-16 are pending in the application.

Applicants acknowledge and thank the Examiner for withdrawing the previously raised rejection of claims 1, 2 and 4-16 under 35 U.S.C. § 112, first paragraph, for alleged failure to comply with the written description requirement.

Applicants also acknowledge and thank the Examiner for withdrawing the previously raised rejections of claims 1, 2 and 4-16 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness.

Response to Rejection of Claims 1, 2 and 4-16 under 35 U.S.C. § 103(a): Piskin in view of Won

The Examiner has rejected claims 1, 2 and 4-16 under 35 U.S.C. § 103(a) as being obvious over Piskin *et al.* (J. Biomat. Sci. Polymer Edn. 1995, 7(4):359-373; "Piskin") in view of Won *et al.* (Science 1999, 283:960-963; "Won"). The Examiner contends that Piskin teaches a method of using copolymer made from PEG-PLA (referred to as PEG/PDLLA by Piskin) to form micelles, wherein the micelles are used to encapsulate doxorubicin and the release of drug is controlled by degradation of the PLA component of the micelles. The Examiner admits that Piskin does not teach the blending of PEG-PLA with PEG-PBD to form micelles. The Examiner further argues that Won teaches that PEG-PBD can be used to form micelles. The Examiner opines that it would have been obvious for an ordinary skilled artisan to form a micelle from a mixture of PEG-PBD and PEG-PLA. Applicants respectfully traverse this rejection, and submit that the combination of the art cited by the Examiner does not render the claims obvious under 35 U.S.C. § 103(a) for the following reasons.

According to the U.S. Supreme Court ruling in *Graham v. John Deere*, 383 U.S. 1 (1960), in making a case for obviousness, the Examiner must: (1) determine the scope and content of the prior art; (2) ascertain the differences between the prior art and the claims at issue; (3) resolve the level of ordinary skill in the pertinent art; and (4) evaluate evidence of secondary considerations. These principles have been reconfirmed by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 USPQ2d 1385 (2007).

In *KSR Int'l Co.*, the U.S. Supreme Court restated the requirements for a finding of obviousness. Encouraging the application of common knowledge and common sense, the Court took care to guard against hindsight bias and *ex post* reasoning and to distinguish the predictable from the unpredictable arts ("If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability." [Emphasis added]). Based on the reference cited by the Examiner, Applicants assert that the rejection of the claims under 35 U.S.C. §103 could only have been made with hindsight bias and *ex post* reasoning.

When applying 35 U.S.C. § 103, the following tenets of patent law must be followed: (1) the claimed invention must be considered as a whole; (2) the references must be considered as a whole; (3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (4) reasonable expectation of success is the standard with which obviousness is determined (MPEP § 2141 II). None of these criteria have been met here.

Piskin does not render obvious the presently claimed methods. Piskin teaches micelles prepared with a copolymer made from PEG-PLA (referred to as PEG/PDLLA by Piskin). Piskin does not teach or suggest the preparation of micelles from a mixture of PEG-PBD and PEG-PLA. Contrary to Piskin, claim 1 recites a method of preparing stable, controlled release PEO-based polymersome vesicles having an amphiphilic high molecular weight PEO-based block copolymer encapsulating membrane, wherein the vesicles encapsulate at least one active agent. A person of ordinary skill in the art would find no teaching, motivation or suggestion in Piskin to

develop a method of preparing micelles comprising PEG-PBD and PEG-PLA, let alone the polymersome vesicles of the present invention.

Won does not cure the deficiencies of Piskin. Won teaches micelles that are made from PEG-PBD copolymer. Won does not teach or suggest that PEG-PBD may be blended with PEG-PLA to form micelles, let alone that PEG-PBD may be blended with PEG-PLA to form polymersome micelles which may encapsulate at least one active agent therein. Therefore, a person of ordinary skill in the art would find no teaching, motivation or suggestion in Piskin in view of Won to arrive at the methods of the present invention.

In another aspect, a person skilled in the art would recognize that Piskin and Won teach micelles that are distinct from each other and from the micelles recited in the present claims in terms of structure and properties. Piskin teaches micelles that are classically sized, with mean radius varying between 24 nm and 56 nm (Table 4, page 368 of Piskin). Piskin's micelles are proposed to be spherical in shape. The copolymers used in the preparation of Piskin's micelles are not polymerizable and have a molecular mass around 10^7 g/mol (Table 4, page 368 of Piskin). On the other hand, Won teaches giant wormlike rubber micelles with cylindrical dimensions of > 1 μm (2nd column, page 961 of Won). The copolymers used in the preparation of Won's micelles are polymerizable and undergo a large increase in average molecular weight upon polymerization: from ~4.9 x 10^3 g/mol (1st column, page 961 of Won) to ~2 x 10^8 g/mol (3rd column, page 962 of Won).

Based on the distinct properties of Piskin's and Won's micelles, a person of ordinary skill in the art would not be motivated to combine these copolymers because there is no evidence or suggestion in Piskin or Won that the combination of these copolymers generates a stable micelle, let alone that these copolymers may be combined to form a polymersome vesicle.

Piskin and Won are silent about the structure of the potentially formed micelle. In contrast, Applicants' claims recite a method of preparing stable, self-

assemblying polyethylene oxide (PEO)-based polymersome vesicles, having a semi-permeable, thin-walled, amphiphilic, PEO-based block copolymer encapsulating membrane.

Piskin and Won are further silent about whether there is an appropriate blend ratio of the copolymers in the potentially formed micelle and what factors should be considered in the selection of such blend ratio. In contrast, Applicants' claims recite a method of preparing stable polyethylene oxide (PEO)-based polymersome vesicles, having an amphiphilic, PEO-based block copolymer encapsulating membrane, comprising the step of determining the appropriate blend ratio (mol %) of a hydrolysable PEO-based block copolymer with at least one polyester component, and at least one inert PEO-based block copolymer with at least one hydrophobic component, to produce amphiphilic PEO-based polymersomes with a desired controlled release rate of the encapsulated encapsulant based upon the blend ratio.

Piskin and Won are also silent about how to effect controlled hydrolysis of the membrane. In contrast, Applicants' claims recite a method of preparing stable, self-assemblying polyethylene oxide (PEO)-based polymersome vesicles, wherein the at least one inert PEO-based block copolymer is selected to effect controlled polyester chain hydrolysis in the membrane, such that when combined with the hydrolysable PEO-based block copolymer, the PEO volume fraction (f_{EO}) and chain chemistry control encapsulant release kinetics from the copolymer vesicles, and further control polymersome carrier membrane destabilization.

Piskin and Won are further silent about how to effect self-assembly of the polymersomes. In contrast, Applicants' claim recite a method of preparing stable, self-assemblying polyethylene oxide (PEO)-based polymersome vesicles, comprising the step of blending the hydrolysable PEO-based block copolymer in aqueous solution together with the at least one inert PEO-based block copolymer to effect self-assembly of the amphiphilic PEO-based polymersomes, without the use of a co-solvent, having the desired controlled release rate of the at least one encapsulant contained therein when the encapsulant is released by hydrolysis-driven membrane poration.

Therefore, the finding that the combined copolymers of the present invention form stable, purely synthetic, self-assembling, controlled release polymersome vesicles, which may be used for controlled transport and delivery of encapsulated active agents, is an unexpected result that would not have been predicted by the teachings of Piskin, Won, or any prior art cited by the Examiner. Piskin in view of Won thus cannot render claims 1, 2 and 4-16 obvious under 35 U.S.C. § 103(a).

In light of the present arguments, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 2 and 4-16 over Piskin in view of Won.

Conclusion

Applicants respectfully submit that the arguments set forth herein evidence that the pending claims are in full condition for allowance. Accordingly, favorable examination of the claims is respectfully requested at the earliest possible time.

Respectfully submitted,

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